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Structure–Activity Relationships of Non-imidazole H_3 Receptor Ligands. Part 1

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Abstract—SAR studies for novel non-imidazole containing H_3 receptor antagonists with high potency and selectivity for rat H_3 receptors are described. A high throughput screening lead, A-923, was further elaborated in a systematic manner to clarify a pharmacophore for this class of aryloxyalkyl piperazine based compounds. © 2002 Elsevier Science Ltd. All rights reserved.

The histamine class of receptors has been a fertile ground for the development of important therapeutic agents. It is well established that allergic conditions can be controlled by blockade of H_1 receptors, while relief of gastric ulcers through modulation of H_2 receptors is highly efficacious therapy.[1] Histamine mediates its action both in the CNS and the periphery through four distinct receptors known to date.[2] Although the histamine-3 receptor (H_3R) was discovered over 15 years ago, the following decade provided minimal medicinal chemistry advancement in non-imidazole based H_3 agents.[3] This slow progress is partially due to the lack of potent, selective, and safe agents which hindered understanding of the H_3R role in pathophysiology and the delay in successful cloning of this receptor.[4] The H_3 receptor was originally described as a presynaptic receptor regulating the synthesis and release of histamine. H_3Rs not only act as autoreceptors, but are also involved in presynaptic regulation of the release of acetylcholine, gamma-aminobutyric acid, dopamine, noradrenaline and serotonin. H_3R modulation could have therapeutic utility in cognitive disorders, including but not limited to attention deficit and hyperactivity disorder (ADHD), and in obesity among other potential benefits.[5] The increasing interest in the therapeutic potential of H_3 agonists and/or antagonists is driving current medicinal chemistry efforts to identify potent, selective, therapeutically efficacious and safe agents for clinical development.[6] A-923 (Fig. 1) was identified from high throughput screening (HTS) of the Abbott compound collection as a ~2 nM affinity ligand at rat H_3R. Its non-imidazole containing features differentiated it from most early H_3 receptor ligands, although during the completion of this work several publications reported new non-imidazole H_3 antagonists with comparable or inferior potency compare to A-923. However, further characterization revealed its poor selectivity versus other histaminergic receptors. We describe here in Part I of a two-part series of Letters (see following manuscript) some pharmacophoric features of these non-imidazole H_3 receptor ligands.[7] A systematic modification of parts A–E of this lead molecule was conducted using parallel synthesis when possible.

Modification of the Carbamate Functionality (section A)

Commercially available phenol **1** (Scheme 1) was treated with 1-bromo-3-chloropropane in the presence of K_2CO_3 in refluxing 2-butanone for 24 h. The resulting *O*-alkyl chloride **2** (obtained in ~95% yield) was further treated, without purification, with *N*-Boc-piperazine to

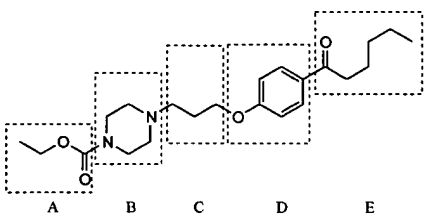

Figure 1.

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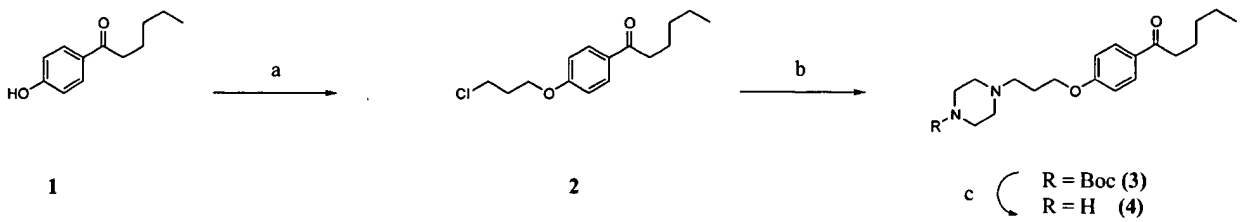


Scheme 1. (a) Cl–$(CH_2)_3$–Br, K_2CO_3, 2-butanone, reflux 24 h; (b) *N*-Boc-piperazine, KI/K_2CO_3, 2-butanone, reflux 72 h; (c) TFA–CH_2Cl_2, 0 °C to rt, 12 h.

Table 1. Binding affinities[a] (pK_i) at rat cortical H_3 and human H_1 and H_2 receptors[9]

Compd:[b] R	H_3	H_1	H_2	R	H_3	H_1	H_2	R	H_3	H_1	H_2
4: H	7.57	5.22	4.84	**17**: CO-Ph	7.44	6.54	4.91	**30**: CO-Et	8.50	5.72	4.5
5: CO_2Me	8.52	5.97	4.92	**18**: CO-2-thiophene	7.79	7.13	4.83	**31**: CO-Pr	8.19	6.06	4.64
6: CO_2Et (A-923)	8.86	6.56	4.90	**19**: CO-5-Me-2-thioph.	7.80	7.01	5.09	**32**: CO-*i*Pr	8.35	5.40	4.53
7: CO_2Bu	7.69	6.24	5.73	**20**: CO-3-Cl-2-thioph.	7.53	7.10	4.71	**33**: CO-cyclopropyl	8.67	5.75	4.50
8: CO_2*i*Pr	8.30	6.51	4.75	**21**: CO-2-furan	7.98	6.40	4.70	**34**: CO-cyclobutyl	8.50	6.45	4.99
9: CO_2iBu	8.00	6.56	5.43	**22**: CO-3-Me-2-furan	8.07	6.98	4.89	**35**: CO-CH_2-Ph	8.00	7.25	5.05
10: CONH-*i*Pr	8.02	5.92	4.95	**23**: CO-2-*N*-Me-pyrrole	8.39	7.25	4.93	**36**: CO-CH_2S-Et	7.96	5.96	4.64
11: CONH-Et	7.67	5.80	4.63	**24**: CO-5-oxazole	7.35	5.37	4.56	**37**: CO-COH$(CH_3)_2$	7.24	4.67	4.61
12: CO-pyrrolidine	8.13	5.98	4.83	**25**: CO-5-imidazole	8.35	6.28	4.71	**38**: Propyl	7.56	5.47	4.56
13: CO-morph.	8.23	5.38	4.75	**26**: CO-2-pyrazine	7.74	5.69	4.33	**39**: CH_2-cycloprop.	7.80	5.65	4.73
14: SO_2Me	7.67	4.58	4.08	**27**: CO-2-pyridine	7.28	6.38	4.73	**40**: Butyl	7.87	6.18	5.12
15: SO_2*i*Pr	7.90	4.95	4.68	**28**: CO-3-pyridine	7.69	6.14	4.22	**41**: Isobutyl	8.03	6.34	5.02
16: SO_2(4-CN)-Ph	7.43	4.87	4.91	**29**: CO-4-pyridine	8.20	6.32	4.65	**42**: CH_2-2-thiazole	7.78	7.22	5.15

[a]Values were estimated from at least three separate competition experiments (SEM ≤ 0.2).
[b]Satisfactory ^1H NMR, MS spectra and elemental analyses were obtained for all new compounds.

give **3** in 75–82% yield after s.g.c. TFA treatment in dichloromethane provided piperazine **4** ready for parallel synthesis (Scheme 1). A group of about 75 *N*-acyl, *N*-alkyl, sulfonamides, sulfonylureas, and ureas were prepared using standard acylation chemistry or reductive amination to give compounds **5–42**. These were assayed in a binding experiment using rat cortex in order to probe the SAR of the H_3 receptor.

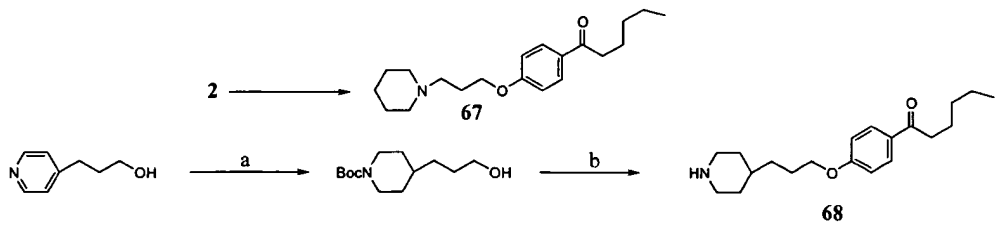
Data from Table 1 indicate a fairly well defined pharmacophore at the piperazine-*N*-substitution. Compound **33** showed the same high affinity for the rat H_3R as the HTS lead A-923; however, with a better selectivity for the human H_1 receptor, several other substitutions altering various physicochemical properties of the molecule were tolerated (i.e., imidazole **25**; morpholine urea **13**). Most other structural alterations resulted in lower H_3 affinities.

Modifications of Sections B–D[8]

The basic piperazine in A-923 was replaced with a variety of amines: morpholine, 2,6-dimethylmorpholine, pyrrolidine, homopiperazine, 4-aminopiperidine, 4-piperidinopiperidine, etc. (e.g., **67**, $H_3R = 7.20$), with no significant improvement in affinity at rat H_3R. More importantly, we demonstrated that exchange of the piperazine basic nitrogen in A-923 to a carbon atom (**68**, Scheme 2) resulted in loss of affinity at the rat H_3R ($pK_i = 4.23$). Additionally, both the length (2-, 3-, and 4-atom linker) and substitution of the 3-carbon chain linker was further substituted with methyl and/or aryl at either the 1-, 2-, or 3-position in both enantiomeric forms. This resulted in no improvement in affinity with minor selectivity towards the *R*-enantiomers at either the 1- or 2-position. The aromatic ring was examined to a lesser degree. In this case, substitutions at the ketone *ortho*-position (–NH_2, –Cl, –F, –OMe) were tolerated, whereas substitutions at *meta*-positions were not additive.

Modification of the Ketone Functionality (Section E)

We next explored the ketone moiety while retaining the ethyl carbamate functionality in order to further explore SAR. We accessed such ketones via two routes (Scheme 2):

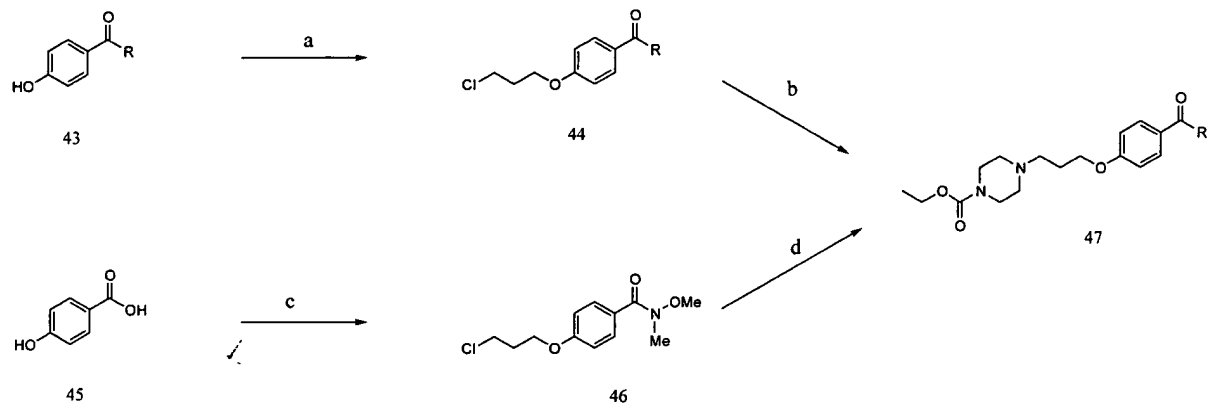


Scheme 2. (a) (i) Rh/Al_2O_3, CH_3OH; (ii) $(Boc)_2$, Hunig's, CH_2Cl_2; (b) (i) **1**, DEAD, PPh_3, THF, 0 °C to rt, 48 h; (ii) TFA–CH_2Cl_2, 0 °C to rt, 12 h.

Table 2. Binding affinities[a] (pK_i) at rat cortical H_3 and human H_1 and H_2 receptors

Compd: R	H_3	H_1	H_2	R	H_3	H_1	H_2	R	H_3	H_1	H_2
48: $-CH_3$	8.30	5.65	4.40	**55**: $-CH_2CH_2CH_3$	8.44	6.13	4.65	**61**: -*p*-Me—S–Ph	7.23	6.35	5.21
49: $-CH_2CH_3$	8.27	5.78	4.25	**56**: $-CH=(CH_3)_2$	7.41	6.45	4.66	**62**: -*p*-MeO–Ph	7.40	6.09	5.08
50: $-C_7H_{15}$	8.43	6.25	5.67	**57**: $-C(CH_3)=CH_2$	7.26	6.01	4.65	**63**: -*p*-*t*Bu–Ph	7.88	6.25	5.81
51: $-C_8H_{17}$	8.10	6.30	5.57	**58**: $-CH_2Ph$	7.16	6.03	4.90	**64**: -*m*-Me–Ph	6.54	6.42	5.43
52: –Cyclopropyl	8.33	5.85	4.10	**59**: – *p*-F–Ph	7.17	6.68	4.37	**65**: -*t*-CH=CH–3′-pyrid.	8.20	6.37	4.60
53: –Cyclohexyl	7.60	6.22	5.10	**60**: -(*o*,*m*)-di-F–Ph	7.60	5.99	4.76	**66**: -*t*-CH=CH–4′-MeO–Ph	8.14	6.21	5.17
54: -*i*-Bu	8.14	6.03	4.16								

[a]Values were estimated from at least three separate competition experiments (SEM ≤ 0.2).



Scheme 3. (a) Cl–$(CH_2)_3$–Br, K_2CO_3, 2-butanone, reflux 24 h; (b) EtOCO-piperazine, KI/K_2CO_3, 2-butanone, reflux 72 h; (c) (i) BnBr, K_2CO_3, DMF; (ii) NaOH; (iii) $(COCl)_2$, cat. DMF, CH_2Cl_2; (iv) MeONHMe, Et_3N, CH_2Cl_2; (v) H_2, Pd/C, CH_3OH; (d) (i) EtOCO-piperazine, KI/K_2CO_3, 2-butanone, reflux 72 h; (ii) RMgX, THF.

commercially available 4-hydroxyphenyl ketones were treated under basic conditions with 1-bromo-3-chloropropane followed by piperazine-*N*-ethylcarbamate to give the desired products. Alternatively, 4-hydroxybenzoic acid was *O*-benzyl alkylated and esterified in a one-pot reaction with $BnBr–K_2CO_3$ followed by hydrolysis. The carboxylic acid, thus obtained, was treated with oxalyl chloride followed with *N*-methoxy-*N*-methylamine to give the corresponding Weinreb amide.[10] Further *O*-debenzylation under hydrogen/Pd conditions followed by *O*-alkylation and *N*-ethylcarbamate piperazine-*N*-alkylation (see above) gave the template amide. The latter was treated with various Grignard reagents to provide the corresponding ketones (Scheme 3).

Table 2 displays binding affinities of compounds where various substitutions were made at the alkyl ketone level. While a range of substituents can be tolerated (long fatty chain to aryl and cinnamoyl type groups), none provided for an enhanced affinity at the rat H_3R.

In summary, SAR data on A-923 have revealed the following: (1) the hydrophobic ketone region can be expanded; (2) small *N*-acyl (**33** or **25**) analogues with a basic site are tolerated; (3) small size chain substitutions are tolerated but do not increase affinity; and (4) the piperazine basic site in A-923 is mandatory for binding/recognition of the ligand at the rat H_3 receptor. From the lead compound it appears that a putative pharmacophore would be a tertiary amine, preferably a 4-atom-long linker and an aromatic ring to be favorable. Substitution patterns around this core system should allow for optimizing physicochemical features to improve oral bioavailability, receptor selectivity, CNS-penetration and in vivo biological efficacy.

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